IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PARIKH et al.

Application No. 09/443,863 Art Unit: 1615

Filed: November 19, 1999 Examiner: G. Kishore

For: DISPERSIBLE PHPOSPHOLIPID STABILIZED MICROPARTICLES

PENDING CLAIMS AFTER AMENDMENTS

50. A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle growth comprising:

a) forming an admixture of a stable aqueous homogenous suspension of micronized surface stabilized primary particles of a water-insoluble or poorly water-soluble drug with a matrix-forming bulking/releasing agent or a mixture of matrix-forming bulking and releasing agents, wherein said stable aqueous homogeneous suspension has a particle size of about 10 μm or less, and each primary particle is a solid drug particle on to which is adsorbed at least one surface modifying agent of which one is a phospholipid;

b) drying said admixture to produce a solid of said surface stabilized primary particles dispersed and embedded throughout a support matrix of said matrix-forming agent or agents, wherein said matrix dissolves or substantially disperses in a rapid disintegration time when in contact with an aqueous environment to release said surface stabilized primary particles into said aqueous environment as a suspension without irreversible particle aggregation and/or particle agglomeration and without particle size growth;

c) optionally course milling and blending said solid with one or more pharmaceutically acceptable excipients to provide a dried powder; and

d) forming said solid or said dried powder into a solid dosage form.

51. The process of claim 50, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of a pharmaceutically acceptable saccharide, a pharmaceutically acceptable polysaccharide, a pharmaceutically acceptable humectant, a pharmaceutically

acceptable cellulose based polymer, combinations thereof, and combinations of these with a pH buffering salt.

52. The process of claim 50, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; maltose; and combinations thereof; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; and combinations thereof with a pH buffering salt.

53. The process of claim 50, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; and maltose; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; microcrystalline cellulose; hydroxymethyl cellulose; hydroxypropyl cellulose; methylcellulose; and combinations thereof, and combinations thereof with a pH buffering salt.

54. The process of claim 50, wherein the matrix-forming agent is present in an amount between 0.1 % w/w and 90% w/w of the aqueous suspension.

55. The process of claim 50, wherein the rapid disintegration time is less than 2 minutes.

56. The process of claim 50, wherein the drug is selected from the group consisting of antifungal agents, immunosuppressive agents, immunoactive agents, antiviral agents, antineoplastic agents, analgesic agents, antiinflammatory agents, antibiotic agents, antiepileptic agents, anesthetic agents, hypnotic agents, sedative agents, antipsychotic agents, neuroleptic agents, antidepressant agents, anxiolytic agents, anticonvulsant agents, antagonist agents, neuron blocking agents, anticholinergic agents, cholinomimetic agents, antimuscarinic agents, muscarinic agents, anti adrenergic agents, antiarrhythmic agents, antihypertensive agents, hormones, and nutrients.

57. The process of claim 50, wherein the drug is selected from the group consisting of fenofibrate, itraconazole, and cyclosporine.

58. The process of claim 50, wherein the drug is present in an amount between 0.1% w/w and 60% w/w of the aqueous suspension.

59. The process of claim 50, wherein the phospholipid is selected from the group consisting of an egg phospholipid, a soybean phospholipid, and combinations thereof.

60. The process of claim 50, wherein the phospholipid is selected from the group consisting of hydrogenated phospholipid, partially hydrogenated phospholipid, and combinations thereof.

61. The process of claim 50, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof.

62. The process of claim 50, wherein the surface modifier is selected from the group consisting of pharmaceutically acceptable nonionic surfactants, pharmaceutically acceptable anionic surfactants, and pharmaceutically acceptable cationic surfactants.

63. The process of claim 50, wherein the surface modifier is selected from the group consisting of casein, gelatin, tragacanth, acacia, and combinations thereof.

64. The process of claim 50, wherein the surface modifier is selected from the group consisting of a pharmaceutically acceptable polyoxyethylene fatty alcohol ether, a sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a poloxamer, a polaxamine, and combinations thereof.

65. The process of claim 50, wherein the surface modifier is selected from the group consisting of glycerol monostearate, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, and combinations thereof.

66. The process of claim 50, wherein the surface modifier is selected from the group consisting of potassium laurate, triethanolamine stearate, sodium lauryl sulfate, an alkyl polyoxyethylene sulfate, sodium alginate, sodium deoxycholate, dioctyl sodium sulfosuccinate, a negatively charged glyceryl ester, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and combinations thereof.

67. The process of claim 50, wherein the surface modifier is selected from the group consisting of benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, and combinations thereof.

68. The process of claim 50, wherein the surface modifier is present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

69. The process of claim 50, wherein the admixture is dried by spray drying, spray coating, or freeze-drying.

70. The process of claim 50, wherein the micronized primary particles are prepared in a particle fragmentation process selected from the group consisting of sonication, milling, homogenization, microfluidization, and antisolvent and solvent precipitation.

71. The process of claim 50, wherein the pharmaceutically acceptable excipient is a tableting aid for compression, a glidant for hard gelatin encapsulation, an effervescent disintegration agent, a dispersant for a dry powder inhaler, or a combination thereof.

72. The process of claim 50, wherein the dosage form is a tablet, a gelatin encapsulation, or a powder.

73. A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle growth comprising:

a) forming an admixture of a stable aqueous homogenous suspension of micronized surface stabilized primary particles of a water-insoluble or poorly water-soluble drug with a matrix-forming bulking/releasing agent or a mixture of matrix-forming bulking and releasing agents, wherein said stable aqueous homogeneous suspension has a particle size of about 10 μm or less, each primary particle is a solid drug particle on to which is adsorbed at least one surface modifying agent of which one is a phospholipid;

b) distributing the admixture of (a) into unit dosage form molds; and

c) freeze-drying said admixture in said unit dosage form molds to produce a solid dosage form of said surface stabilized primary particles dispersed and embedded throughout a support matrix of said matrix-forming agent or agents, wherein said matrix dissolves or substantially disperses in a rapid disintegration time when in contact with an aqueous environment to release said surface stabilized primary particles into said aqueous environment as a suspension without irreversible particle aggregation and/or particle agglomeration and without particle size growth.

74. The process of claim 73, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of a pharmaceutically acceptable saccharide, a pharmaceutically acceptable polysaccharide, a pharmaceutically acceptable humectant a pharmaceutically acceptable cellulose based polymer, combinations thereof, and combinations of these with a pH buffering salt.

75. The process of claim 73, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; maltose; and combinations thereof; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; and combinations thereof with a pH buffering salt.

76. The process of claim 73, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; and maltose; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; microcrystalline cellulose; hydroxymethyl cellulose; hydroxypropyl cellulose; methylcellulose; combinations thereof, and combinations thereof with a pH buffering salt.

77. The process of claim 73, wherein the matrix-forming agent is present in an amount between 0.1 % w/w and 90% w/w of the aqueous suspension.

78. The process of claim 73, wherein the rapid disintegration time is less than 2 minutes.

79. The process of claim 73, wherein the drug is selected from the group consisting of antifungal agents, immunosuppressive agents, immunoactive agents, antiviral agents, antineoplastic agents, analgesic agents, antiinflammatory agents, antibiotic agents, antiepileptic agents, anesthetic agents, hypnotic agents, sedative agents, antipsychotic agents, neuroleptic agents, antidepressant agents, anxiolytic agents, anticonvulsant agents, antagonist agents, neuron blocking agents, anticholinergic agents, cholinomimetic agents, antimuscarinic agents, muscarinic agents, anti adrenergic agents, antiarrhythmic agents, antihypertensive agents, hormones, and nutrients.

80. The process of claim 73, wherein the drug is fenofibrate, itraconazole, or cyclosporine.

81. The process of claim 73, wherein the drug is present in an amount between 0.1% w/w and 60% w/w of the aqueous suspension.

82. The process of claim 73, wherein the phospholipid is selected from the group consisting of an egg phospholipid, a soybean phospholipid, and combinations thereof.

83. The process of claim 73, wherein the phospholipid is selected from the group consisting of hydrogenated phospholipid, partially hydrogenated phospholipid, and combinations thereof.

84. The process of claim 73, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof.

85. The process of claim 73, wherein the surface modifier is selected from the group consisting of pharmaceutically acceptable nonionic surfactants, pharmaceutically acceptable anionic surfactants, and pharmaceutically acceptable cationic surfactants.

86. The process of claim 73, wherein the surface modifier is selected from the group consisting of casein, gelatin, tragacanth, acacia, and combinations thereof.

87. The process of claim 73, wherein the surface modifier is selected from the group consisting of a pharmaceutically acceptable polyoxyethylene fatty alcohol ether, a sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a poloxamer, a polaxamine, and combinations thereof.

88. The process of claim 73, wherein the surface modifier is selected from the group consisting of glycerol monostearate, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, and combinations thereof.

89. The process of claim 73, wherein the surface modifier is selected from the group consisting of potassium laurate, triethanolamine stearate, sodium lauryl sulfate, an alkyl polyoxyethylene sulfate, sodium alginate, sodium deoxycholate, dioctyl sodium sulfosuccinate, a negatively charged glyceryl ester, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and combinations thereof.

90. The process of claim 73, wherein the surface modifier is selected from the group consisting of benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, and combinations thereof.

91. The process of claim 73, wherein the surface modifier is present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

96. A rapidly dispersing solid therapeutic dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle growth comprising particles of a water-insoluble compound, the water-insoluble particles being surface stabilized with one or more surface modifiers of which at least one is a phospholipid and having a particle size of about 10 μm or less, the surface-stabilized particles dispersed throughout a bulking matrix optionally also including a releasing agent, wherein when the solid therapeutic dosage form is introduced into an aqueous environment, the bulking/releasing matrix is substantially completely disintegrated and the surface stabilized water insoluble particles are released in an unaggregated and/or unagglomerated state to form a stable aqueous suspension.